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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/051357	International filing date *(day/month/year)* 05.07.2004
Priority date *(day/month/year)* 10.07.2003	
International Patent Classification (IPC) or both national classification and IPC C07D401/04, C07D471/14	
Applicant AKZO NOBEL N.V.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	9
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Relevant documents**

The following documents **D1-D3** are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US-A-4 062 848 (VAN DER BURG WILLEM JACOB) 13 December 1977 (1977-12-13)

D2: WO 00 62782 A (SINGER CLAUDE ;TEVA PHARMA (IL); LIBERMAN ANITA (IL); FINKELSTEIN) 26 October 2000 (2000-10-26)

D3: SELDITZ U ET AL: 'Direct enantiomeric separation of mianserin and 6-azamianserin derivatives using chiral stationary phases' JOURNAL OF CHROMATOGRAPHY A, ELSEVIER SCIENCE, NL, vol. 803, no. 1-2, 17 April 1998 (1998-04-17), pages 169-177, XP004117830 ISSN: 0021-9673

2. **Novelty**

The present application claims an one-step process for the preparation of enantiomerically pure mirtazapine of formula (I) comprising ring closure of a compound of general formula (II) with enantiomeric excess by treatment with a suitable acid (claims 1-9). A method for the selection of an acid or an acid/solvent combination suitable for the process of claim 1 is also claimed (claim 10). This process is in general defined by the same technical features as the process of the present claim 1.

Prior art D1 discloses a ring closure process for the preparation of racemic mirtazapine (Examples I and IV) followed by an optical resolution of mirtazapine using (-)O,O-dibenzoyltartaric acid (Example XIX).

D2 discloses a ring closure process for the preparation of racemic mirtazapine starting with racemic compounds of formula IV which corresponds with the formula (II) of the present application.

D3 discloses an optical resolution of mirtazapine (6-azamianserin; formula 2) using Chiralpak AD column (Table 3).

Since none of the prior art documents D1-D3 discloses the starting compounds of formula (II) with enantiomeric excess, the subject-matter of the present claims 1-10 appears novel in view of D1-D3, according to Article 54(1) and (2) EPC.

2. **Inventive step**

The problem underlying the present application is seen in the provision of an alternative process for the preparation of enantiomerically pure mirtazapine of formula (I).

The closest prior art represented by D1 discloses a two-steps process comprising
1. a ring closure of racemic compounds of formula II which corresponds with the formula (II) of the present application and
2. a resolution of racemic mirtazapine obtained in the first step.

The difference between D1 process and that of the present application resides in that the starting compounds used in the present process are present in an enantiomeric excess and not in a racemic form.

The solution to the problem stated above is seen in the provision of the process described in the present claim 1, in which process the starting compounds of formula II are used in an enantiomeric excess and not in the racemic form. Such a solution seems to be obvious to the person skilled in the art in view of document D1 which explicitly suggests using optically active compound of formula II instead of the corresponding racemic starting material (column 6, lines 53-59).
Therefore, the subject-matter of the present claim 1 does not involve an inventive step, according to Article 56 EPC.
The dependent process claims 2-4 are also considered not involving inventive step, since the additional technical features described therein are known in the art.

Claim 2: Using a suitable acid in the absence of a solvent is known from D1 (Examples I.4. and IV) and D2 (Examples 1-3).

Claim 3: Using a protic acid is also known from D1 and D2 (use of conc. H_2SO_4 in the same Examples as stated above).

Claim 4: Use of polyphosphoric acid is suggested by the both prior art documents D1 (column 2, paragraph 1 and 2) and D2 (claim 3).

The dependent process claim 5 defines particularly the ratio between polyphosphoric acid and the compound of formula (II). Although definition a such a ratio has not been found in the cited prior art, the skilled person seeking for the optimal reaction conditions would try to find the best ratio between polyphosphoric acid and the compound of formula (II). An optimization of a reaction conditions in the said way is regarded as an every day practice of a person skilled in the art. Since it has not been shown in the present application, that the ratio 5:1 claimed in the present claim 5 leads to a better results then a reaction in which the said ratio is different from 5:1, an inventive step of the present claim 5 cannot be acknowledged.

The dependent process claims 6-9 introduce a novel technical feature in the process of the present claim 1, namely the use of a suitable acid and an organic solvent in combination. The subject-matter of the said claims could be considered as involving an inventive step, when certain improvement of the present process over the prior art processes can be seen. Such an improvement is indeed demonstrated by the present Examples 1-3, in which the yields of 99,2-99,7% are higher then the best yield of the prior art process (Example 3 of D2, 95%). However, it has also been noticed that not every organic solvent used in the ring closure leads to higher yields. E.g. the present Examples 9 and 10 in which ethanol and dichloromethane, respectively are used as a solvent provide (S)-mirtazapine in yields 59% and 62%, respectively. Since the process claims 6-8 comprise organic solvents, which do not improve the yield of the ring closure step, they are considered not inventive.

The present claim 10 does not involve an inventive step from the following reasons:

The subject-matter of claim 10 is a method for the selection of an acid or an acid/solvent combination suitable for the process of claim 1. It is I in general defined by the same technical features as the process of the present claim 1. Additionally, it comprises determining a loss of enantiomeric excess by the reaction and identifying an acid or acid/solvent combination. The said method for the selection is considered obvious for the person skilled in the art, because skilled person knowing the fact that not every acid is suitable for the reaction of claim 1 would try to identify the best acid or acid/solvent combination while detecting the changes in the reaction conditions.

Having regard to what has been stated above, solely the process claim 9 which specify the solvent used as being *N*-methylpyrrolidinone or DMF does involve an inventive step, according to Article 56 EPC.

Re Item VIII

Certain observations on the international application

The following inconsistency between the description and the claims according to Article 6 PCT has been found in the present application. According to the description on page 4, lines 29-31 and on page 5, paragraph 2, some of the combinations of acid/solvent are not suitable for the process presently claimed. However, such statements are not involved in the present claims. The said inconsistency throws doubt on the extent of the protection south for the present application..